FORMULARY Criteria for Using Pravastatin and
NONFORMULARY Criteria for Using Fluvastatin, Fluvastatin XL, Atorvastatin or Rosuvastatin in Veteran Patients
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence. The content of the document is dynamic and will be revised as new clinical data become available. The purpose of this document is to assist practitioners in clinical decision making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

The Department of Veteran's Affairs National Formulary now includes 3 HMG Co-A Reductase Inhibitors (statins): 1) simvastatin (high potency-able to reduce LDL-C by 40% or more), 2) lovastatin, and 3) pravastatin as an option for patients receiving potent inhibitors of CYP 3A4.

All of the available statins (lovastatin, simvastatin, fluvastatin, atorvastatin, pravastatin and rosuvastatin), when administered alone, have been associated with infrequent myotoxic adverse effects ranging from myalgia and myopathy to rhabdomyolysis.[1,15] Factors that may increase the risk for myotoxicity with statins are higher dosages, drug-drug interactions, other myotoxic drugs (e.g. fibrates) and renal impairment.[2-5]

There is a lack of evidence to support a difference in the rate of myopathy or rhabdomyolysis for a particular statin when combined with fibrates and/or lipid lowering doses of niacin (≥1 gram/day). As a result, these criteria will focus on drug-drug interactions involving statins combined with drugs having the same metabolic pathway (e.g. CYP 3A4, 2C9, etc.).

The primary safety concern, in this case, arises from a drug-drug interaction occurring when potent CYP 3A4 inhibitors (e.g. macrolide antibiotics, azole antifungals, cyclosporine, protease inhibitors) are combined with CYP 3A4 metabolized statins (e.g. lovastatin, simvastatin or atorvastatin (nonformulary)). These drug combinations can increase blood levels of the affected statin and may further increase the risk of muscle toxicity. However, combination of these potent inhibitors with non-CYP 3A4 metabolized statins (e.g. pravastatin, fluvastatin (nonformulary) or rosuvastatin (nonformulary)) does not increase blood levels of these statins theoretically affording an additional margin of safety.

Fluvastatin is primarily metabolized via CYP 2C9 and may be vulnerable to interactions with drugs known to inhibit CYP 2C9 metabolism (e.g. amiodarone, omeprazole, metronidazole, fluvoxamine). However, many of these drug interactions with fluvastatin are only theoretical and their clinical significance is not known. In 2002, authors queried the Food and Drug Administrations (FDA) adverse event reporting system database to determine the number of reported cases of statin-associated rhabdomyolysis over a 29 month period (November 1997-March 2000). Of the 601 reported cases, fluvastatin was implicated in only 1.7% of cases and none of those cases involved the combination of fluvastatin with a CYP 2C9 inhibitor.[6] Rosuvastatin is also metabolized via CYP 2C9 and may be vulnerable to interactions with drugs known to inhibit CYP 2C9 metabolism.[15] As with fluvastatin, these interactions are only theoretical and the clinical significance is not known. Pravastatin is not significantly metabolized via the CYP isoenzyme system and is therefore not affected by drugs inhibiting metabolism via these pathways.[1,7,8]

All patients receiving treatment with statins should be advised to report any unexplained muscle pain, tenderness or weakness regardless of statin used or concomitant drugs. Patients experiencing any of these symptoms should be advised to discontinue their lipid therapy immediately and providers should obtain a CK level, if clinically indicated.

There have been reports of excessive anticoagulation in patients receiving statins (lovastatin, simvastatin, fluvastatin and rosuvastatin) in combination with warfarin. As a result, the international normalized ratio (INR) should be monitored closely when statins are initiated, switched to a different statin or discontinued in patients stabilized on warfarin. These patients should also be warned to observe for signs of bleeding.[14,15]

Formulary Criteria for Using Pravastatin (non CYP 3A4 metabolized statin)

- Patients requiring a statin and long-term treatment with an agent(s) known to be a potent CYP 3A4 inhibitor (including but not limited to: clarithromycin, erythromycin, cyclosporine, protease inhibitors, delavirdine, itraconazole, fluconazole, verapamil, amiodarone, etc.).
- Patients receiving lovastatin or simvastatin who require short-term treatment with a potent CYP 3A4 inhibitor should have their statin therapy temporarily withheld or closely monitored during their course of therapy. (In general, there is no need to switch to pravastatin in these patients unless the course of CYP 3A4 inhibitor therapy becomes prolonged, e.g. longer than 2-4 weeks).
- Patients experiencing muscle pain or weakness, without elevation in creatine kinase (CK), on formulary statins (simvastatin or lovastatin) may receive a trial of pravastatin with close follow up.

Nonformulary Criteria for using Fluvastatin or Fluvastatin XL in Place of Simvastatin, Lovastatin or Pravastatin (One must be checked to be eligible)

- In patients who are receiving cyclosporine or gemfibrozil and require statin therapy, providers can consider using fluvastatin (as fluvastatin concentrations are less affected by these drug combinations).
- Patients requiring the use of a non CYP 3A4 metabolized statin and are experiencing muscle pain or weakness, without elevation in CK, on pravastatin (may receive a trial of fluvastatin or fluvastatin XL with close follow up)

Nonformulary Criteria for Using Atorvastatin in Place of Lovastatin or Simvastatin

- Patients who have not met their LDL-C goal on maximum doses or maximally tolerated doses of simvastatin and are not receiving potent CYP 3A4 inhibitors.

Nonformulary Criteria for Using Rosuvastatin in Place of Lovastatin, Simvastatin or Pravastatin (One must be checked to be eligible)

- Patients who have not met their LDL-C goal on maximum doses or maximally tolerated doses of simvastatin.
- Patients with an inadequate LDL-C lowering response to maximum dose pravastatin in patients receiving potent CYP 3A4 inhibitors. (The initial dose in these patients should be 5 mg daily.)

- The VA Medical Advisory Panel (MAP) has recommended that rosuvastatin 20 mg daily generally be the maximum daily dose of rosuvastatin in the veteran population until more safety data are available for the 40 mg dose. However, the 40 mg dose can be considered only after confirmation of compliance with the lipid-lowering regimen; after a careful assessment of the benefits and risks in an individual patient; and only if the patient has not met their LDL-C goal (VA/DoD Dyslipidemia Guideline) on 20 mg daily. Factors that can increase the risk for serious adverse events (myopathy and rhabdomyolysis) should be considered in the risk assessment. These factors include but are not limited to: increasing statin doses, drug-drug interactions, hypothyroidism, frailty, advanced age and renal impairment. In those patients on rosuvastatin 40 mg daily, the MAP recommends baseline and periodic urinary and renal function monitoring. If unexplained, persistent proteinuria is noted in a patient receiving rosuvastatin 40 mg daily, the manufacturer recommends reducing the dose of rosuvastatin.
- Rosuvastatin is not a substrate for cytochrome P450 3A4 (CYP 3A4) and therefore is not vulnerable to interactions with potent CYP 3A4 inhibitors. However, there are other interactions and situations that can result in clinically significant increases in rosuvastatin's serum concentrations. As a result, the manufacturer has recommended dose limits or dosing guidance for rosuvastatin in these individuals (e.g. cyclosporine, gemfibrozil, antacids, severe renal impairment, hemodialysis, Asian Americans). See table below on page 3.

Rosuvastatin Dosing in Special Circumstances*

Special Circumstance	Starting Daily Dose	Maximum Daily Dose
Those predisposed to myopathy (advanced age, renal impairment, hypothyroidism)	5 mg	20 mg
Severe renal impairment (crcl<30 ml/min)	5 mg	10 mg
Hemodialysis recipients	5 mg	5 mg
Combined with cyclosporine	5 mg	5 mg
Combined with gemfibrozil	5 mg	10 mg
Asians	5 mg	20 mg

*The VA Medical Advisory Panel (MAP) has recommended 20 mg to be the maximum daily dose of rosuvastatin in the veteran population until more safety data are available for the 40 mg daily dose. However, the 40 mg daily dose can be considered if a provider deems necessary. However, baseline and periodic urinary and renal function monitoring should be performed in these individuals.

Dose Conversion of Fluvastatin to Pravastatin, Metabolic Fate of Statins and Summary of Criteria

Approximate Equivalent Daily Doses of Statins: LDL-C Lowering Data from Clinical Trials.[11]						
	Lovastatin	**Simvastatin**	**Fluvastatin**	**Pravastatin**	**Atorvastatin**	**Rosuvastatin**
	20 mg	10 mg	40 mg	20 mg	--	--
	40 mg	20 mg	80 mg	40 mg	10 mg	--
	80 mg	40 mg	--	**	20 mg	--
	--	80 mg	--	--	40 mg	10 mg
	--	--	--	--	80 mg	20 mg
Metabolic Fate:						
	Lovastatin	**Simvastatin**	**Fluvastatin**	**Pravastatin**	**Atorvastatin**	**Rosuvastatin**
Primary Metabolic Enzymes	CYP 3A4	CYP 3A4	CYP 2C9	Sulfation	CYP 3A4	CYP 2C9, 2C19
Lipophilicity	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic	Hydrophilic
Formulary Status of Statins						
	Lovastatin	**Simvastatin**	**Fluvastatin**	**Pravastatin**	**Atorvastatin**	**Rosuvastatin**
Formulary or Nonformulary	**Formulary**	**Formulary**	**Nonformulary**	**Formulary**	**Nonformulary**	**Nonformulary**
Recommendations For Using a Particular Statin			**Criteria for NF Use:** Can consider fluva in those patients receiving cyclosporine or gemfibrozil , as fluvastatin conc. are less affected when combined with these agents.	**Criteria for Use:** Those on potent CYP 3A4 inhibitors.	**Criteria for NF Use:** Inadequate LDL-C lowering response to max dose simvastatin and <u>not</u> receiving potent CYP 3A4 inhibitors.	**Criteria for NF Use:** For patients not meeting their LDL-C goals on max dose simva. Or, inadequate LDL-C lowering response to max dose pravastatin and receiving potent CYP 3A4 inhibitors. Initial dose in these patients should be 5 mg qd.
	Lovastatin	**Simvastatin**	**Fluvastatin**	**Pravastatin**	**Atorvastatin**	**Rosuvastatin**
Monthly Cost ($) (30 day supply)	20 mg 7.50 40 mg 7.50 80 mg 15.00 (2x40 mg)	10 mg 1.50 20 mg 1.80 40 mg 1.80 80 mg 2.70	Current (BIG4): 20 mg 39.00 40 mg 39.00 80 mg XL 50.10 FSS: 20 mg 40.20 40 mg 50.40 80 mg XL 69.00	20 mg 2.40 40 mg 3.00 80 mg 6.00 (2x40 mg)	10 mg 45.60 20 mg 67.80 40 mg 70.20 80 mg 70.20	5 mg 34.50 10 mg 34.50 20 mg 34.50 40 mg 34.50

**If a patient is receiving Fluvastatin XL 80 mg daily, conversion to pravastatin 80 mg daily can produce similar reductions in LDL-C (At 4 weeks, mean change in LDL-C was 37% for pravastatin 80 mg vs. median LDL-C change of 38% for fluvastatin XL 80 mg).[12-13] Immediate release fluvastatin should be used only in doses of 20 or 40 mg daily. In those patients requiring 80 mg daily, conversion to fluvastatin XL is recommended. *Prices are as of 7-18-07 and do not consider tablet splitting.

*Potent CYP 3A4 inhibitors include but are not limited to: azole antifungals (fluconazole, ketoconazole, itraconazole), macrolides (erythromycin and clarithromycin), protease inhibitors, delavirdine, amiodarone, verapamil, cyclosporine and nefazodone.

For more detailed information on statins refer to the following website:
http://www.pbm.va.gov/reviews/HMGStatins04-09-03.pdf . **For more detailed information on rosuvastatin, refer to the following website:** http://vaww.pbm.va.gov/drugmonograph/Rosuvastatin.pdf

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